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TITLE: Effects of Time of Day, Age and Gender on the Ability to  
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13. ABSTRACT (Maximum 200)  Seven adults, 2 women in the follicular phase or the menstrual cycle and 5 men, were studied. We intend to provide information relating to age, gender, and the phase of the menstrual cycle when the study is complete. The question addressed to date, regards the mechanism explaining the diurnal urinary response to a water load of 12 ml/kg lean body mass. We observed a 20% greater ( $P < 0.05$ ) diuresis in response to a water load during the daytime compared to nighttime, despite a slightly lower resting plasma osmolality (Posm) during the nighttime. The plasma osmolality resulting after the drink was similar during the daytime and nighttime. Despite this, plasma vasopressin levels were lower after the drink during the daytime compared to the nighttime ( $P < 0.05$ ), and the levels were reduced relative to predrink controls for a longer time during the daytime ( $P < 0.05$ ). Free water loss accounted for most of the diuretic response as expected, and the increased cumulative urine flow appears to result from a prolonged decrease in urine osmolality and increase in free water clearance during the daytime compared to the nighttime.					
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*John R. Clay Jr.* 15 March 96  
PI - Signature Date

## TABLE OF CONTENTS

	<i>Page</i>
Introduction	1
Experimental Methods	2
Results	4
Cumulative urine flow (Fig 1)	4
Plasma osmolality (Fig 2)	5
Free water and osmotic clearances (Fig 3)	6
Urine Osmolality (Fig 4)	7
Plasma vasopressin (Fig 5)	7
Urinary vasopressin (Fig 6)	8
Conclusions and study projections	8
Bibliography	9
Paid personnel	11
Publications	11

## INTRODUCTION:

The recent observation (1) that there is an impaired ability to excrete a water load at night in adult men is the first demonstration of a diurnal pattern in water handling *per se*. It has been previously shown that the diuresis and natriuresis associated with either head-out immersion in water or in response to infusion of 2 liters of normal saline is reduced at night (2), but the difference between daytime and nighttime responses was almost entirely due to differences in osmotic (as opposed to free water) clearance (2,3). The mechanisms that lead to the difference in water handling have not been determined. In those original experiments, the major differences between the daytime and nighttime urine output and osmolalities became noticeable 90 minutes after the challenge, and were definitely evident by 2 hours. Measurements of plasma osmolality and ADH were only taken at 60 min following the challenge, and therefore could not provide any information on the potential role of the ADH system in the decreased nocturnal diuretic response. In order to define a potential role of ADH in the diurnal response difference to water loading, measurements of plasma osmolality and ADH must be obtained between 60 and 180 minutes following the drink. There are two probable ADH and osmolality responses to such a water challenge: (1) Plasma osmolality and ADH will respond together and either remain lower during the daytime, thereby causing the extended period of decreased urine osmolality and increased urine flow, or both will decrease similarly during daytime and nighttime, but there would be a comparative refractoriness of the kidney to ADH during the daytime. (2) Plasma osmolality and plasma vasopressin may not respond in parallel. The plasma osmolality may be similarly decreased during daytime and nighttime, but the vasopressin response may be reduced at night.

The circadian pattern of urine flow, high during the day and low during the night, has been thought to be due to changes in plasma ADH, quoted to be low during the day and high during the night. Although this pattern of ADH has been reported (5), the exceptions to this report are numerous. Most current observations report ADH patterns to be high during the daytime and low during the night in ambulatory subjects(6,7,8,9), but these reports are often ignored (10).

In addition to ADH, cortisol has a definite role in controlling the handling of free water by the body. Cortisol greatly enhances the ability to excrete a water load (4). Serum cortisol levels exhibit a circadian rhythm, being highest at 0800 H and lowest at midnight. This rhythm has been reported to normally begin at about 6 months of age (12), but basal cortisol levels appear to progressively increase and reach adult levels around puberty (13). It is important to recognize that the circadian rhythm of cortisol favors water retention at night and mirrors the circadian rhythm of urine output. The importance of this is suggested by studies in subjects who are given a steady dose of cortisone lose the circadian rhythm of urinary water and sodium excretion (11).

Although a number of factors have been proposed as causing enuresis, a study by Norgaard, et al (10) found that 9 of 11 patients studied had normal bladder capacities, but that 7 of the 11 did not have lower urine flows at night. Therefore, enuretic children represent a population where the adult circadian rhythm of reduced urine flow at night is not completely developed.

The present experiment will indirectly test the hypothesis that cortisol may play a role in the adult circadian rhythm of reduced urine flow at night. We hypothesize that in

the pediatric enuretic subjects, the normal adult cortisol rhythm will not be present, but will be found in non-enuretic children.

The response of adult women to a water load has not been compared to men. The relationship of ADH to plasma osmolality has been studied in various conditions in female rats that were pregnant or pseudopregnant, or infused with estrogen and progesterone combinations, and was found to be unchanged (14). However, the effectiveness of ADH in causing an antidiuresis is greatly influenced by the presence of estrogen or progesterone. Share and Crofton (15) recently reviewed this topic, and it appears that estrogen and progesterone have separate, additive effects in inhibiting the effects of ADH on the kidney. This appears to be through an inhibition of ADH-induced production of cyclic AMP(16). This clearly implicates that estrogen and progesterone have an effect on water balance which is distinct from other effects which they have on sodium balance (estrogen causes sodium retention, while progesterone has a minimal sodium loosing effect). These observations suggest that if a standardized oral water load is administered acutely to men and women, the body distribution and reduction in plasma osmolality should be similar. The subsequent reduction in plasma ADH should also be similar, but the proportional volume of water excreted should be greater in women. Since this effect appears to be dependent upon estrogen and progesterone levels, the effect should be greatest in adult females during the luteal phase, and the difference between males and females would not be expected in the children.

#### EXPERIMENTAL METHODS:

The schedule is as shown below. The daytime and nighttime experiments will be separated by more than 24 hours. Breakfast and supper will have been eaten at 0600 and 1800 in the laboratory and fluid intake limited to one cup of fluid, and similar caloric and fat contents in the meals. No alcohol, smoking or heavy exercise was allowed on the day of the experiment. Because of the late hour of the nighttime test, 1900 until 2300, we will allow the children to spend the night at TAMC if so desired, without charge. Also, the children will have only hourly urine collections.

Table 1: Schedule

Daytime	Nighttime	Activity or Event
0600	1800	Void urinary bladder (this request will be relayed to the subjects telephonically)
0700	1900	Subjects report to study area. Body weights and skin folds are determined. Urine #1 is collected. Adult subjects are prepared with a 21 ga. "Angiocath" intravenous line with heparinized (1:1 heparin [1000 units/ ml] to normal saline) saline in the line.
0800	2000	Subjects void bladders. Urine collection #2. Record blood pressure and heart rate and temperature. Obtain blood sample #1 (20 ml for adults, or optional 10 ml for children)

(Table 1 continued)

Daytime	Nighttime	Activity or Event
0800 - 0815	2000 - 2015	Drink water, 15° C, 12 ml/kg lean body weight
0830	2030	Collect urine sample #3, & blood sample #2 (12 ml each for remainder of test)
0900	2100	Collect urine sample #4 & blood sample #3
0930	2130	Collect urine sample #5 & blood sample #4
1000	2200	Collect urine sample #6 & blood sample #5
1030	2230	Collect urine sample #7 & blood sample #6
1100	2300	Collect urine sample #8 & blood sample #7

Evaluations to be made on specimens.

Blood. (only in adult studies)

Hematocrit (microcentrifugation)

Plasma (only in adult studies, and for initial samples in consenting children)

Estrogen (adult females only, only on initial sample)

Progesterone (adult females only, only on initial sample)

Aldosterone (only on initial sample)

Dehydroepiandrosterone (only on initial sample)

Cortisol

ACTH (initial samples only)

Plasma Renin Activity (initial samples only)

Antidiuretic hormone

Epinephrine

Norepinephrine

Osmolality (Freezing point depression)

Sodium (ion specific electrode)

Potassium (ion specific electrode)

Creatinine (Jaffe reaction , auto analyzer)

Urine (all subjects)

Volume

Creatinine

Osmolality

Sodium

Potassium

Cortisol

Antidiuretic hormone

Aldosterone (initial sample only)

DHEA (initial sample only)

Epinephrine

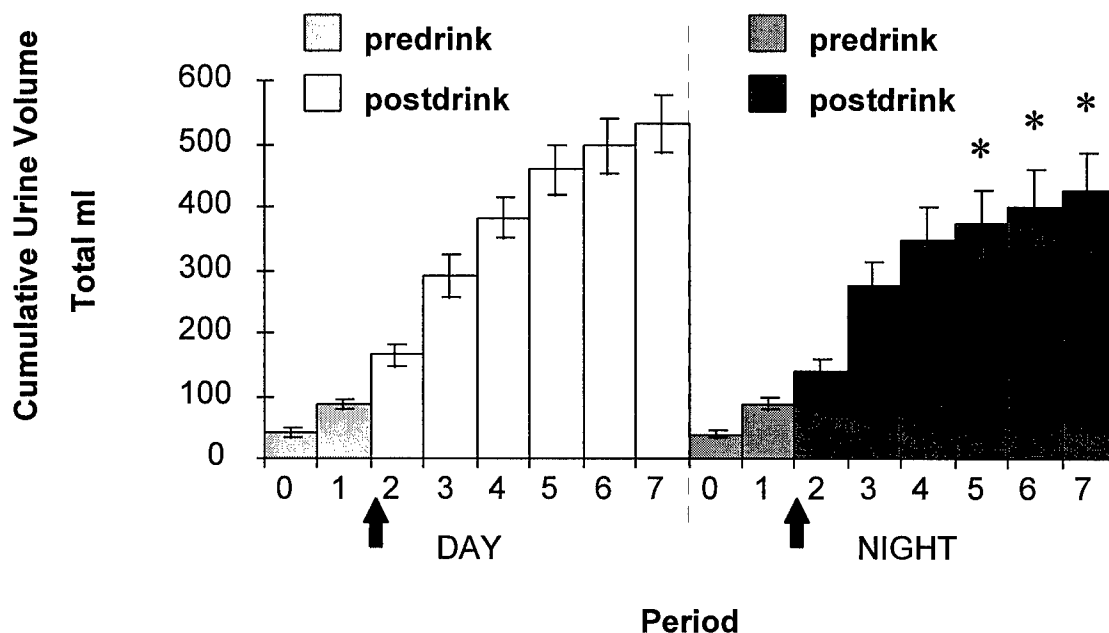
Norepinephrine

Calculated values in adults include, creatinine clearance as an index of glomerular filtration rate, osmotic and free water clearances, and filtration fraction of sodium and potassium through out the experiment.

## RESULTS:

No pediatric studies have been conducted, and since so few female subjects have been completed, we can make no statements about pediatric, gender or menstrual cycle effects on the responses to a water load at this time. We have conducted studies on two females in the follicular phase of the menstrual cycle, and none in the luteal phase, and we have conducted studies on 5 men. All of the analyses on these studies is now complete (and accounts for some differences in the data that resulted from the one-month difference in time between the Annual Progress Report and this "Final Report").

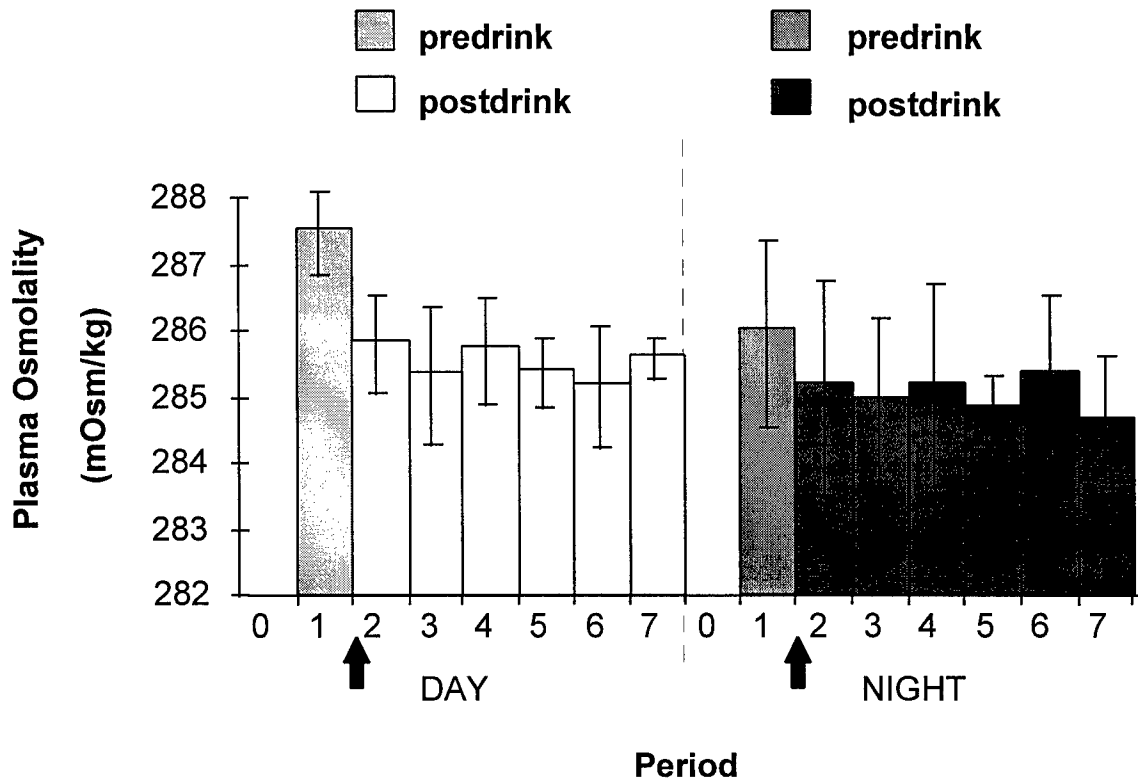
So far, the data are consistent with the previously published observation that the cumulative urine volume produced in response to a drink of water is greater during the daytime than the nighttime (Figure 1). The cumulative urine flow during the daytime is significantly greater than nighttime beginning at the fourth 30-min urine collection following the drink and continuing through 180 min postdrink.



**Figure 1.** Cumulative urine flow shown in 30-min increments in 5 male subjects and 2 female subjects in the follicular phase of the menstrual cycle, in response to a water load of 12 ml/kg lean body mass, at daytime (samples 2 - 7, open bars) and nighttime (samples 2 - 7, dark shaded bars). \* =  $P < 0.05$  compared to corresponding value during the daytime. ↑ = point at which water drink was given.

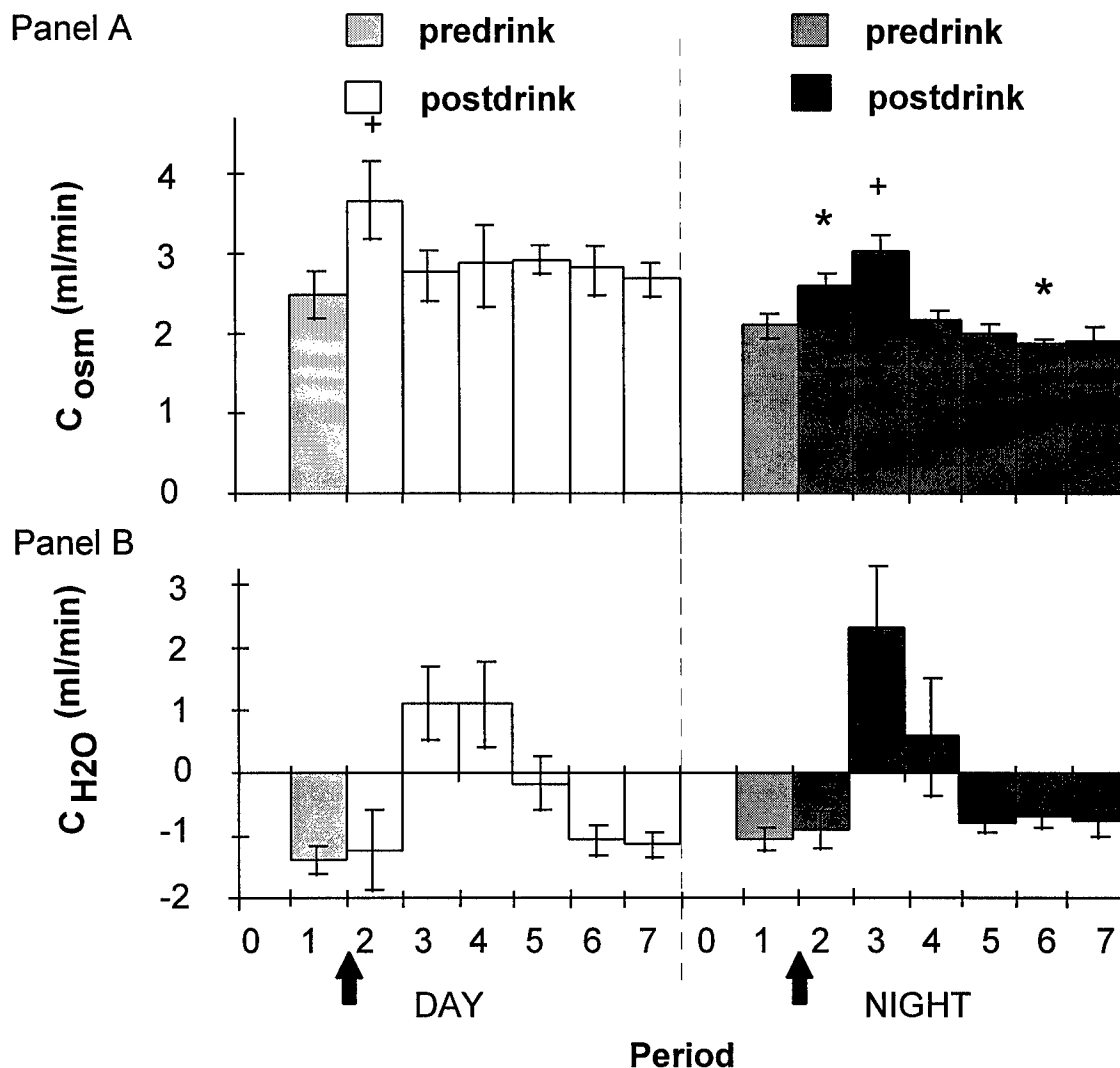
The increased urine flow during the daytime is not due to a state of greater hydration. By controlling the food and fluid intake before both daytime and nighttime experiments, the plasma osmolality was not greater at night. (Figure 2). In fact, the

average plasma osmolality was slightly lower (not statistically significant) prior to the water load when given during the nighttime. It is noteworthy that plasma osmolality was not different between the daytime and nighttime experiments at any period following the drink. Geelen, et al (17), when documenting an oropharyngeal inhibition of vasopressin release in humans, showed that plasma osmolality is reduced about 1 mOsm/kg at 30 min and 60 min post drink (10 ml/kg). The drop we observed during the daytime is slightly greater, but is consistent with their observation.



**Figure 2.** Plasma Osmolality is shown in response to the drink of water during the daytime and nighttime. The same statistics were conducted on these data, and the same subjects are included in these data. No differences were detected over time or between day and night. No plasma samples were taken at 0 sample periods.

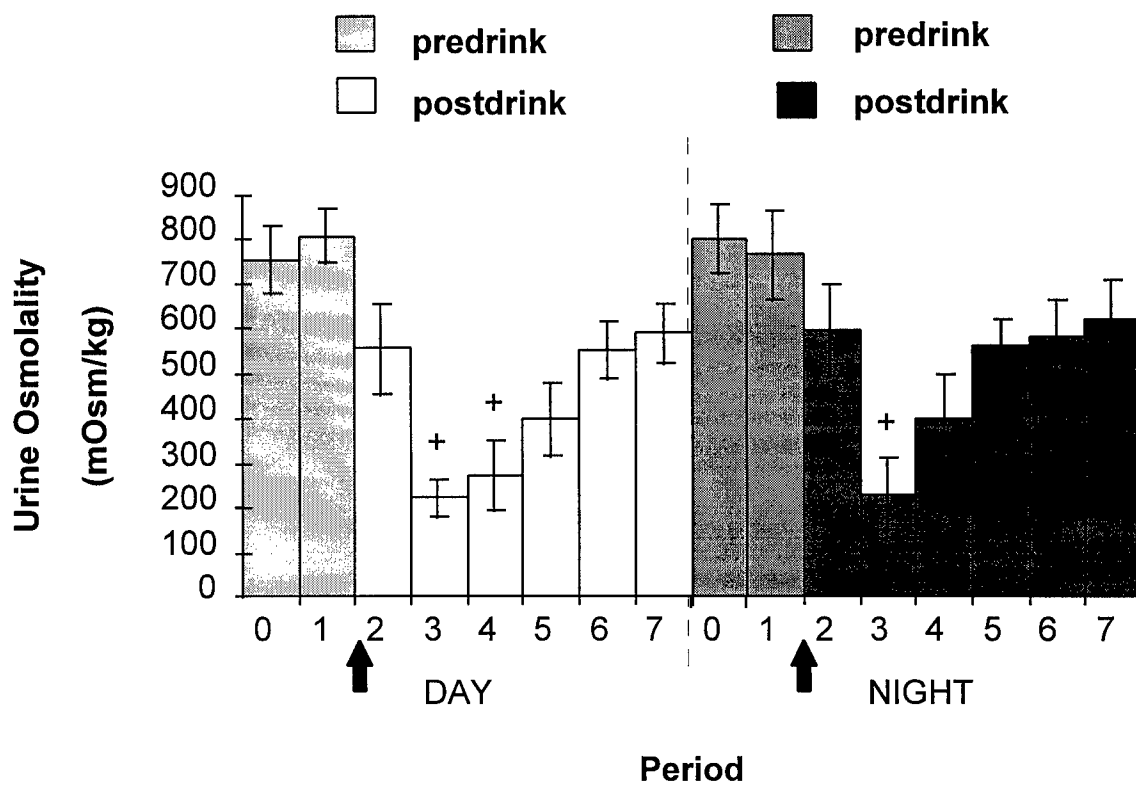
If the mechanism of this increased urinary response during the daytime is primarily due to increases in free water losses as opposed to osmotically induced water losses, we would postulate that its effect on urine flow would probably be via reduced vasopressin. If so we should observe a greater reduction in urine osmolality during the daytime. Figure 3 shows the importance in free water clearance ( $CH_2O$ ) in the diuretic response. Note that,  $CH_2O$  increases about 2.5 ml/min and the increase, remaining at about 1 ml/min, is extended to 1.5 h. By comparison, the increase in  $Cosm$  is only 1 ml/min and lasts only 30 min. It also appears that the increase in  $CH_2O$  lasts longer during the daytime. In fact, the integrated response of increased free water loss is greater during the daytime.



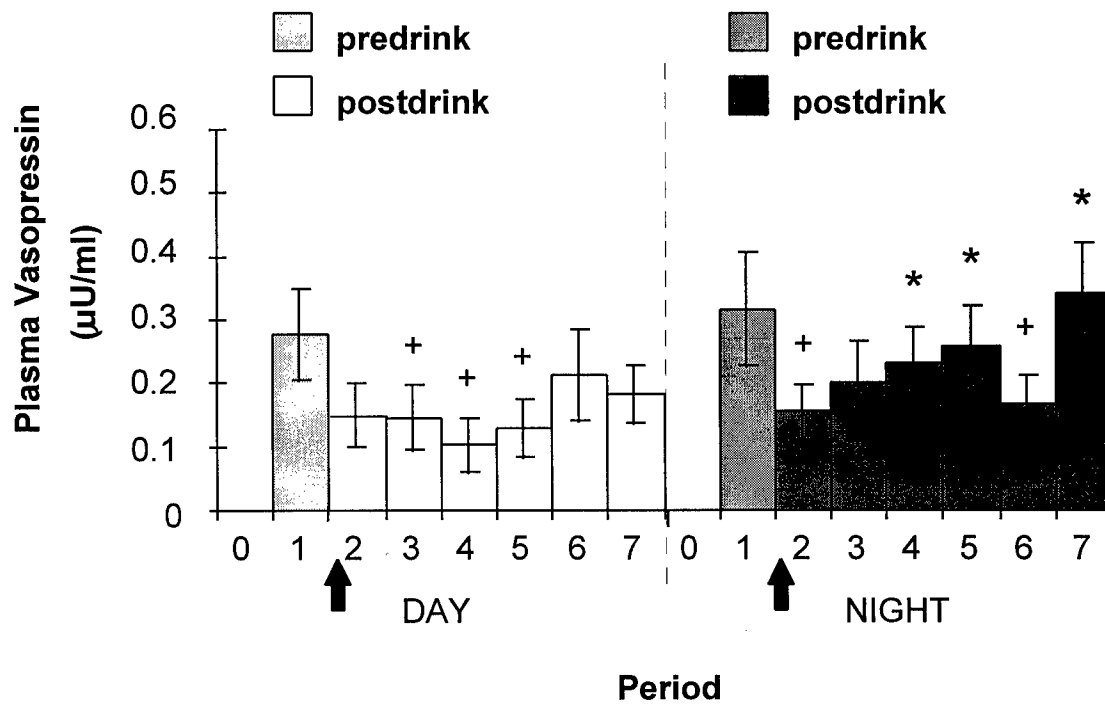
**Figure 3.** Osmotic clearance ( $C_{osm}$ ), panel a, and free water clearance ( $C_{H_2O}$ ), panel b. Note the increase in  $C_{H_2O}$  following the drink accounts for a majority of the diuresis. Also, the response tends to last longer in the daytime experiments. + =  $P < 0.05$  compared to corresponding predrink control, and \* =  $P < 0.05$  compared to corresponding daytime value.

The urine osmolality ( $U_{osm}$ ), shows a typical response with a statistically significantly more prolonged reduction in osmolality during the daytime than the nighttime (Figure 4). This effect is identical to our previous findings (1). That is, the osmolality of the urine is not reduced to a lower osmolality, it is reduced for a longer period at the same low osmolality.

The question now becomes, is this due to decrease in vasopressin? This has never been previously determined, and the current studies indicate that the mechanism may be vasopressin related. Figure 5 shows the plasma vasopressin ( $P_{avp}$ ). The plasma vasopressin shows a greater and more prolonged reduction during the daytime. Furthermore, after the first hour following the drink at nighttime, plasma vasopressin is significantly greater than during the daytime during 3 of 4 30 minute-periods.

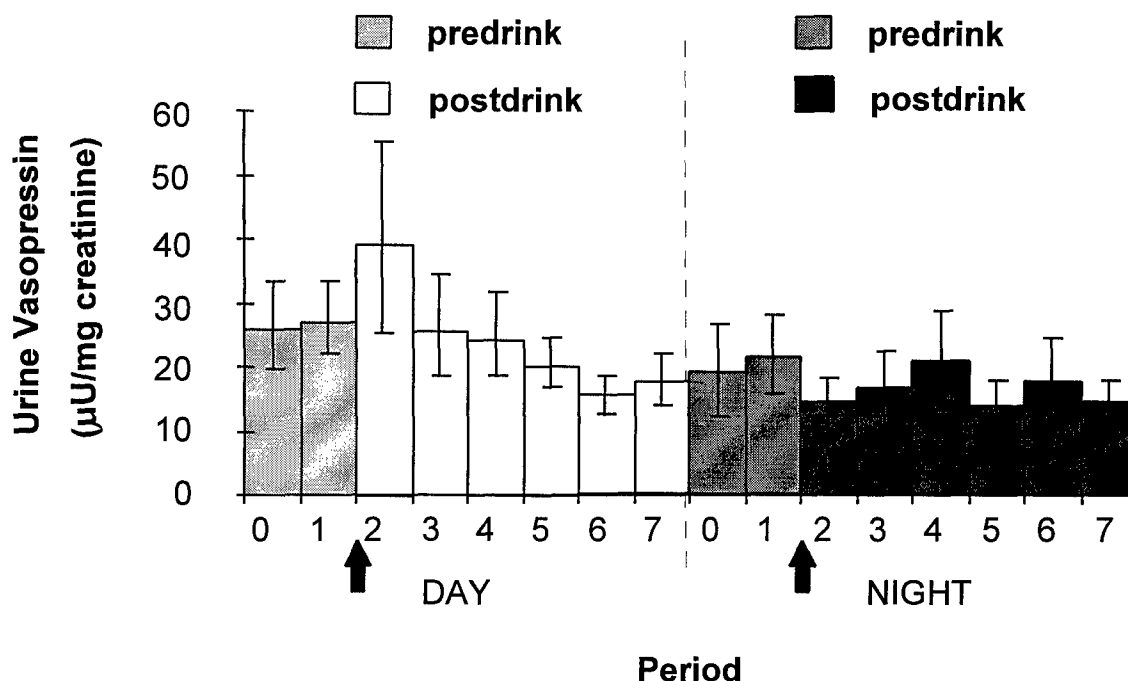


**Figure 4.** Urine osmolality (Uosm, mOsm/kg H<sub>2</sub>O). Note the more prolonged decrease during the daytime. + =  $P < 0.05$  compared to either of the corresponding predrink 1-hour control collection periods.



**Figure 5.** Plasma vasopressin (μU/ml plasma). Note the more prolonged decrease during the daytime.

Another important observation may shed some light on the current controversy regarding the circadian rhythm of vasopressin. Figure 6 shows the urinary excretion of vasopressin in response to the water load. In some respects, the urinary vasopressin response reflects the plasma vasopressin response in that during the daytime there appears to be a decrease that is sustained, but this is not as prominent in the nighttime. The big difference, however, is that overall, vasopressin excretion is lower at nighttime, but this is not true for the plasma concentrations of vasopressin. This means that the urinary clearance of vasopressin is reduced at night.



**Figure 6.** Urinary excretion of vasopressin ( $\mu\text{U}/\text{mg}$  of creatinine). No statistically significant changes were detected over time or between day and night experiments. Overall, by contrast comparisons, the nighttime excretion of vasopressin is lower than the daytime.

#### CONCLUSIONS:

At this point our data support previous observations, and suggest a vasopressin-mediated difference in the day/night response to a water load. That is, the water drink during the daytime causes a more prolonged reduction in plasma osmolality and consequently a more prolonged decrease in plasma vasopressin concentration than during the nighttime. This would explain the previously observed and presently confirmed observation that urine osmolality is decreased for a more prolonged time during the daytime than the nighttime in response to an identical water load.

The present data indicate that, at least in part, the mechanism explaining the prolonged decrease in urinary osmolality is a prolonged decrease in plasma vasopressin concentration. The question now becomes, what causes plasma vasopressin to stay down

longer in response to a water load during the daytime than the nighttime? Plasma osmolality, the obvious possible explanation, is not different between daytime and nighttime. There are two likely possibilities. First, the data are compatible with a reduced urinary clearance of vasopressin at night. This would contribute to the increased plasma levels of vasopressin we observed. Secondly, cortisol can cause an increase in osmotic threshold for vasopressin release (18). Thus, for any given plasma osmolality, vasopressin will be lower when cortisol is present. Therefore, it may be that the circadian rhythm of cortisol, high during the morning, causes vasopressin to be slightly higher at nighttime. Since vasopressin seems to be involved in the day/night response, we may find some differences due to gender and age in subsequent experiments on this protocol, and initially supported by this grant.

The data presented in this report were completed by September 30, 1995. We have since completed two women in both phases of menstrual cycle, and have two others enrolled with one experiment on each. Although the experiments on the men were successfully conducted, a mishap in the lab caused some vasopressin samples (for two subjects and for both daytime and nighttime experiments) to be lost, so more male subjects will be recruited.

The delay in the initiation of the grant delayed the acquisition of personnel, and shortened their stay. Therefore the completion of the study will take longer than one year which we just completed in February. We expect that all phases of the study, including the pediatric phase, will be completed near August 1996.

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APPENDIX: none

PERSONNEL RECEIVING PAY FROM THIS GRANT:

Linda Crosswhite (Graduate assistant)  
Tim Mickel (Graduate assistant)

PUBLICATIONS:

Claybaugh, J. R., A.K. Sato, L.K. Crosswhite, and L.H. Hassell. Reduced diuretic response to water intake at night is accompanied by increased vasopressin in humans. Experimental Biology Meetings, Washington D.C., April 14-18, 1996 (abstract).



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FOR THE COMMANDER:

*Phyllis M. Rinehart*  
PHYLLIS M. RINEHART

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